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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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PILLSBURY WINTHROP SHAW PITTMAN, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER	
NICKOL, GARY B	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 03/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/743,739	HANNA ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-46* is/are pending in the application.

4a) Of the above claim(s) *44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-43,45 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Re: Hanna *et al.*

Date of priority: 09-18-1997

DETAILED ACTION

Election/Restrictions

The response filed on 01-09-2006 to the restriction requirement of 12-06-2005 has been received. Applicant has elected the species of "cancer" (Claim 42) and "papillomavirus E7" (Claim 45) without traverse.

Claim 44 was withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 38-43, and 45-46 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 45 recites the limitation "the antigen" in Claim 38. There is insufficient antecedent basis for this limitation in the claim because claim 38 does not mention any particular antigen but rather to a type of response, "antigen-specific", by cytotoxic T-cells.

Claims 38-45 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. Essentially,

there is no active step that facilitates an "antigen-specific" cytotoxic T-lymphocyte (CTL) response. The specification does not appear to teach that the antagonist of the immunosuppressive factor induces the antigen-specific CTL. Thus, the enhancement cannot take place without specifically including the omitted agent or molecule that invokes the CTL response. See MPEP § 2172.01.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38-43, and 45-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for enhancing an antigen-specific cytotoxic T-lymphocyte response in a subject in need thereof comprising administering an antagonist of TGFβ in conjunction with the papillomavirus E7 protein or melanoma tumor associated antigens, does not reasonably provide enablement for the method as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a method for enhancing an antigen-specific cytotoxic T-lymphocyte response in a subject in need thereof comprising administering an antagonist of an immunosuppressive factor, such as the immunosuppressive factor TGFβ. The claims are further inclusive of inducing an antigen-specific CTL response including providing any antigen (Claim 46) or specific antigens (Claim 45).

The specification teaches (page 4) that the invention is drawn toward increasing the therapeutic efficacy of a tumor vaccine by both inducing a CTL response and by neutralizing an immunosuppressive factor such as TGFβ or IL-10. Thus, the claims can be broadly interpreted as a method of treating cancer in a human patient comprising administering *any* antigen that may elicit a CTL response in combination with an antagonist of *any* immunosuppressive factor. However, the generic induction of effective CTL responses in patients with tumors (i.e. immunotherapy) is highly unpredictable. For example, Bodey *et al.* (Anticancer Research, July-August 2000, Vol. 20, pages 2665-2676) teach that cancer vaccine approach to therapy is based on the notion that the immune system could possibly mount a rejection strength response against the neoplastically transformed cell conglomerate. However, due to the low immunogenicity of tumor associated antigens (TAAs), downregulation of MHC molecules, the lack of adequate costimulatory molecule expression, secretion of immunoinhibitory cytokines, such expectations

are rarely fulfilled (abstract). Further, while peptide vaccination against tumor antigens can induce powerful systemic CTL responses, the majority of patients do not achieve tumor regression (page 2673, column 1). For example, Lee *et al.* (Jnl. Immunology, 1999, Vol. 163, pages 6292-6300) teach that while peptide-based vaccines can generate a quantifiable T-cell-specific immune response in peripheral blood mononuclear cells (PBMCs) of cancer patients, the response did not associate with a clinically evident regression of metastatic melanoma. Lee *et al.* suggest that this significant limitation may be due to the extent ("quantitative capacity") rather than the quality of the response (column 2, page 6299). Also, Gaiger *et al.* (Blood, Volume 96, No. 4, August 2000, pages 1480-1489) chose to evaluate the Wilm's tumor antigen (WT1) as a potential immunotherapeutic as it is well known in the art that WT1 protein expression is more abundant in leukemia cells than in normal hematopoietic ells. However, WT1 peptide immunization did not show any effect on tumor growth in-vivo (Figure 10, page 1486).

Thus, while neutralizing or eliminating potential immunosuppressive factors, like TGF-β, may ultimately lead to an enhancement of the CTL response, the specification provides insufficient guidance or objective evidence that all such antigen-specific responses would predictably increase the therapeutic efficacy of a tumor vaccine. In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to practice the invention as broadly claimed. Thus, only a method of enhancing an antigen-specific cytotoxic T-lymphocyte response in a subject in need thereof comprising administering an antagonist of TGFβ in conjunction with the papillomavirus E7 protein or melanoma tumor-associated antigens, but not the full breadth of the claims, is enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 38-40, 46 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 94/09815 (SEGARINI *et al.*, May 1994, IDS).

Segarini *et al.* teach a method of increasing the effectiveness of a vaccine comprising administering an antagonist of an immunosuppressive factor wherein said antagonist is a TGFβ antagonist wherein the TGFβ antagonist is a TGFβ binding polypeptide (see page 8, lines 23+; and page 46, claim 19). The administration of a "vaccine" would enhance an antigen-specific cytotoxic T-lymphocyte response. According to the online version of Stedman's Medical Dictionary, a "vaccine" encompasses any preparation intended for active immunologic prophylaxis.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 38-39, 42-43, 45-46 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent Application No. 2002/0004052 A1 (BERD *et al.*, June 7, 1995).

Berd *et al.* teach a method of treating cancer or neoplasms comprising administering an antagonist of an immunosuppressive factor. Specifically, Berd *et al.* teach the administration of

tumor cells or tumor cells extracts [para 41] which include antigens isolated from a hapten modified cancer cell or a cell membrane isolated from a hapten modified cancer cell. It is further noted that these peptides include a protein encoded by cancer oncogenes [para 42]. Berd *et al.* further teach the administration of an antagonist of an immunosuppressive factor administered sequentially or concurrently, and in any order with the adjuvant composition [para 46] wherein said antagonist is cyclophosphamide [para 9]. Further, as evidenced by Matar *et al.* (Eur. J. Cancer, May 2000, Vol. 36 No. 8, pages 1060-6, IDS), cyclophosphamide would effectively antagonize the immunosuppressive factor, TGFβ. Berd *et al.* further teach various cancers that can be treated by the method, including melanoma, breast, lung, colon, kidney, and prostate cancers [para 40]. Further, although the prior art does not specifically teach the antigens listed in Claim 45, the administration of the melanoma cell vaccine as taught by Berd *et al.* would inherently induce an antigen-specific cytotoxic T-lymphocyte response specific for melanoma-associated antigens such as gp100, MART-1/MELAN A, MAGE, BAGE, etc. Thus, while Berd *et al.* do not specifically characterize the antigens to which the CTL response is directed at, the claimed functional limitation would be an inherent property of the referenced method since the specification discusses (page 13) a wide variety of melanoma associated antigens. Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 571-272-0835. The examiner can normally be reached on M-Th, 8:30-5:30; alternate Fri., 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary B. Nickol Ph.D.
Primary Examiner
Art Unit 1642

GBN

GARY B. NICKOL, PH.D.
PRIMARY EXAMINER